REMARKS

Claims 1, 7-10, 14 and 15 are currently pending. Claim 1 is directed to a method of inhibiting expression of survivin in human cells or tissues. Claim 7 as amended is directed to a method of inhibiting cytokinesis in a cell. Claim 8 as amended is directed to a method of inhibiting progression of the cell cycle in a cell. Claim 9 is directed to a method of inhibiting proliferation of cells. Claim 10 is dependent from claim 9 and specifies that the cells are cancer cells. Claims 14 and 15 are dependent from claim 9 and are directed to the further use of chemotherapeutic agents.

Applicants acknowledge with thanks the telephonic interview kindly granted to the undersigned attorney on December 2, 2003. Applicants and Examiner discussed the sole outstanding rejection of all pending claims 1, 7-10, 14 and 15 under 35 U.S.C. § 112, first paragraph as assertedly lacking enablement for *in vivo* therapeutic applications. During the interview, the Applicants presented *in vivo* data confirming the specification's statements regarding antitumor activity of anti-survivin antisense compounds. In addition, Applicants and Examiner discussed amending claims 7 and 8 to clarify the nature of the "modulation" as interfering with cytokinesis and cell cycle progression, respectively.

The accompanying Declaration under 37 C.F.R. §1.132 presents *in vivo* data showing that an illustrative anti-survivin antisense compound SEQ ID NO: 87 (ISIS 23722) was able to inhibit growth of two different types of tumor cells in a xenograft tumor model that is accepted in the art as predictive of human therapeutic efficacy. Nude mice were implanted with human glioblastoma and human melanoma cells, respectively, and were treated with either ISIS 23722 or a mismatch control oligonucleotide three days after implantation. See paragraph 3 of the declaration. The antisense compounds were administered intraperitoneally in the first study and intravenously in the second study. Tumor volume was measured twice weekly. The results showed that treatment with ISIS 23722 produced a statistically significant delay in tumor growth, in each study, compared to animals treated with vehicle or the mismatch control oligonucleotide. See paragraph 4 and Figures 1 and 2 of the declaration.

These data confirm the specification's statements that anti-survivin antisense compounds will inhibit proliferation of cancer cells, particularly human cancer cells. As noted during the interview, Applicants have shown that inhibition of survivin expression *in vitro* is correlated to inhibition of cell proliferation *in vitro* and inhibition of xenografted human tumors *in vivo*. ISIS 23722 was shown to inhibit survivin mRNA levels *in vitro* (Example 16, Table 2, at page 57, line 3.). This inhibition of survivin expression was shown to result in antiproliferative effects on human cancer cells *in vitro*; ISIS 23722 inhibited proliferation of human fibrosarcoma cells by up to 77% and breast carcinoma cells by up to 69% (Example 22, pages 66-67). In addition, inhibition of survivin expression was shown to promote apoptosis in HeLa cells (Example 20, page 64) and to interfere with cytokinesis and the cell cycle (Example 21, pages 64-65). Similar effects on other cell types, such as melanoma, lung carcinoma, and endothelial cells were reported in Li et al., *Nature Cell Biol.*, v. 1:461-466 (1999) at page 461, 2nd col. (reference C3 on Form-1449 filed October 24, 2003, which was published after the priority date of the instant claims).

The observed inhibition of survivin expression *in vitro* was shown to be observed *in vivo* when anti-survivin antisense compound was applied to human skin grafts in immunodeficient mice (Example 25, pages 69-70). Finally, the data in the accompanying declaration show that the *in vitro* antiproliferative effects of ISIS 23722 are linked to *in vivo* inhibition of growth of human glioblastoma and human melanoma tumors in xenograft models.

During the interview, Applicants also discussed the breadth of data supporting enablement of the present claims. A variety of delivery routes have been tested and found to be effective, *i.e. in vitro* delivery to cell culture, topical delivery as in Example 25, and intraperitoneal or intravenous delivery as in the accompanying declaration. Applicants have also shown that a variety of different antisense compounds can produce highly significant reductions in survivin expression. The specification shows in Examples 15-18 (and Tables 1-5) that different antisense compounds of varying oligonucleotide sequence, targeting disparate regions of the survivin gene, were able to produce 30% or more, or 50% or more, inhibition of survivin mRNA levels. Finally, Applicants have shown that anti-survivin

antisense compounds are able to inhibit proliferation of a variety of unrelated cancer types, including fibrosarcoma, breast carcinoma, glioblastoma and melanoma.

Applicants respectfully submit that one of ordinary skill in the art would be able to carry out the claimed methods without undue experimentation and that the rejection of the pending claims for asserted lack of enablement may properly be withdrawn.

CONCLUSION

For these reasons, Applicants respectfully submit that all pending claims 1, 7-10, 14 and 15 are allowable. Reconsideration of the outstanding rejection is respectfully requested and an early notice of allowance is solicited.

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Respectfully submitted,

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